An 8 year old, female neutered cross breed dog was presented to the R(D)SVS Internal Medicine Service following a 2 month history of ataxia and collapsing episodes which occurred only at exercise. The owners reported that the ataxia improved after feeding and that she was clinically normal between episodes. Her owners also reported that she had gained weight. The referring veterinary surgeon had documented hypoglycaemia on one occasion following a previous collapsing episode. The dog’s owners had started feeding sugary foods in an effort to prevent further collapsing episodes.

On presentation, the dog was bright, alert and responsive. She was in good body condition with a body condition score of 6/9. Oral mucous membranes were pink, with a capillary refill time of 1 second. Heart rate was 125 beats per minute, with synchronous femoral pulses of good quality, a regular rhythm, and no murmurs detected. The dog was panting, but there was no associated increase in effort. Thoracic auscultation and percussion were within normal limits. Abdominal palpation and peripheral lymph nodes were unremarkable. Rectal temperature was 37.9°C. Neurological examination was unremarkable.

1) What are your main differentials for this case?

2) How would you evaluate the case further?
1) Differential diagnosis

The main problems detected in the history and physical examination were the history of ataxia/collapsing episodes at exercise and the previous finding of hypoglycaemia by the referring veterinary surgeon.

The differentials for ataxia/collapsing episodes include:

- Metabolic/endocrine eg insulinoma, hyopadrenocorticism, hepatic encephalopathy, phaeochromocytoma
- Cardiovascular eg pericardial effusion, arrhythmia
- Neuromuscular eg myasthenia gravis
- Neurological eg vestibular disease, intervertebral disc disease
- Musculoskeletal disease eg hip dysplasia, osteoarthrits, polymyositis
- Haematological eg anaemia, polycythemia, episodic haemorrhage eg ruptured splenic haemangiosarcoma
- Respiratory eg laryngeal paralysis

The differentials for hypoglycaemia include:

- Insulinoma
- Extrapancreatic neoplasia eg hepatocellular carcinoma, carcinoma
- Hepatic disease
- Hypoadrenocorticism
- Idiopathic
- Polycythemia
- Dietary

Based on absence of cardiovascular, musculoskeletal, neurological and respiratory abnormalities on physical examination, the most likely differential diagnoses were considered to be metabolic/endocrine diseases, notably insulinoma and hypoadrenocorticism.
2) Evaluation

- Routine haematology and biochemistry profiles were unremarkable except for a marked hypoglycaemia of 1.8mmol/l (ref 3-8mmol/l). The blood sample was processed immediately following collection ruling out iatrogenic causes of hypoglycaemia.
- A blood sample for serum insulin concentrations was taken concurrently when blood glucose was measured and was 12.9 ui/ml (ref 11.6-29.0 ui/ml)
- A serum fructosamine concentration of 290umol/l (ref 49-225umol/l) was documented. This was unexpected since we would have anticipated a lower value with her documented history of hypoglycaemia.
- An ACTH stimulation test was unremarkable ruling out hypoadrenocorticism as a cause of hypoglycaemia.
- A CT scan of her thorax and abdomen revealed a triangular 0.9x0.6cm markedly contrast enhancing area in the craniodorsal aspect of the left pancreatic lobe. No evidence of metastatic disease was reported.

Based on these results an insulinoma was suspected

Initial Management

- Medical management
  5mg prednisolone q 12 hours was prescribed to antagonise the action of insulin and stimulate hepatic glucenoogenisis and glycogenolysis.

- Dietary management
  Owners were advised that the dog should be fed 4-6 times daily. In addition a diabetic diet was dispensed for the dog. This diet is in high protein and complex carbohydrate. This was done to prevent triggering massive insulin release in response to feeding more simple which can cause worsening of her hypoglycaemia. A clear exception to this management is during times of clinically apparent hypoglycaemia where IV dextrose bolus +/- feedings simple sugars is required to overcome acute clinical signs associated with hypoglycaemia.

Further investigations and Management

Once her clinical signs were stabilised with medical management the dog returned to the R(D)SVS for surgical excision of the pancreatic mass. Histopathology confirmed our suspected diagnosis of insulinoma. No metastasis lesions were grossly evident at the time of surgery and no evidence of metastasis was found in liver biopsy samples.
Discussion

Insulinomas are uncommon tumours of beta pancreatic cells which have the ability to produce and secrete insulin independently of normal neurohumoral mechanisms which control normal glucose homeostasis. Middle aged dogs are most commonly affected. No clear sex or breed predisposition has been established.

Clinical signs occur as the result of hypoglycaemia and elevated concentrations of counter-regulatory hormones such as catecholamines. Common clinical signs include neurological symptoms such as ataxia, weakness and seizures, weight gain and polyphagia due to effects on insulin on appetite and fat metabolism.

Diagnosis of canine insulinoma can be difficult. The most common laboratory finding in dogs with hypoglycaemia but glucose levels can fluctuate and a single, normal glucose levels cannot be used to exclude insulinoma. Concurrent blood glucose and blood insulin levels are more helpful. A diagnosis of insulinoma can be made based on documenting hypoglycaemia in the presence of inappropriate serum insulin concentrations. Insulin levels may be within normal reference intervals but these are still considered to be inappropriate in a hypoglycemic animal as insulin concentrations should be low due to the negative feedback effects of low serum glucose concentrations on insulin production.

Fructosamine concentrations can be used as an indicator of chronic hypoglycaemia and significantly lower fructosamine concentrations have been reported in dogs with insulinomas (Loste, Marca et al. 2001; Mellanby and Herrtage 2002). Interestingly this dog had a high fructosamine level. This may be due to the owners feeding her sugary food before exercise to try to prevent further collapsing episodes.

Imaging techniques can be helpful in diagnosis insulinoma and for establishing whether grossly apparent metastatic disease is present. However, the sensitivity of abdominal ultrasound for the diagnosis of insulinoma can be as low as 28%. Computed tomography (CT) has been shown to be valuable in the detection of insulinomas and was therefore used in this case. (Robbena, Pollak et al. 2005)

Insulinomas are malignant and commonly metastasis to the liver and lymph nodes. It is suspected that a high proportion of dogs will have metastasis at the time of diagnosis but can only be confirmed in around half of dogs at the time of surgery (figure 1). For this reason, further monitoring for metastasis is recommended and the prognosis is guarded. Liver biopsies are commonly collected at the time of surgery to assess for microscopic metastatic lesions. Although surgery is not typically curative it can extend survival times and improve the efficacy of concurrent medical management. Median survival times for dogs with insulinoma treated surgically are 12 months, although one study reports median survival times of up to 18 months (Polton, White et al. 2007). Medical management alone (diet, frequent feeding and steroids) can also be considered. Median survival times for dogs treated medical vary in the literature from 2.5 to 7 months.


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Figure 1: Intraoperative image of pancreas in a dog undergoing exploratory surgery for a suspected insulinoma. The arrow points to a nodular lesion on the pancreas which was excised and later confirmed histologically to be an insulinoma.